Morbidity of radiotherapy carcinoma prostate

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1. **Gastro-intestinal effects (GI)**
2. **Genitourinary effects (GU)**
3. **Erectile dysfunction (ED)**

Acute GI effects

Acute GI effects - RTOG grade

Grade I

- Increased stool frequency
- Rectal discomfort
- Change in quality of bowel habit

- No drugs required

Grade II

- Diarrhoea, needs drug
- Mucus discharge, no pads
- Pain rectum, needs drug, occasional narcotic

Grade III

- Diarrhoea, needs I.V.
- Mucus / blood discharge, pads needed
- Abdominal distension

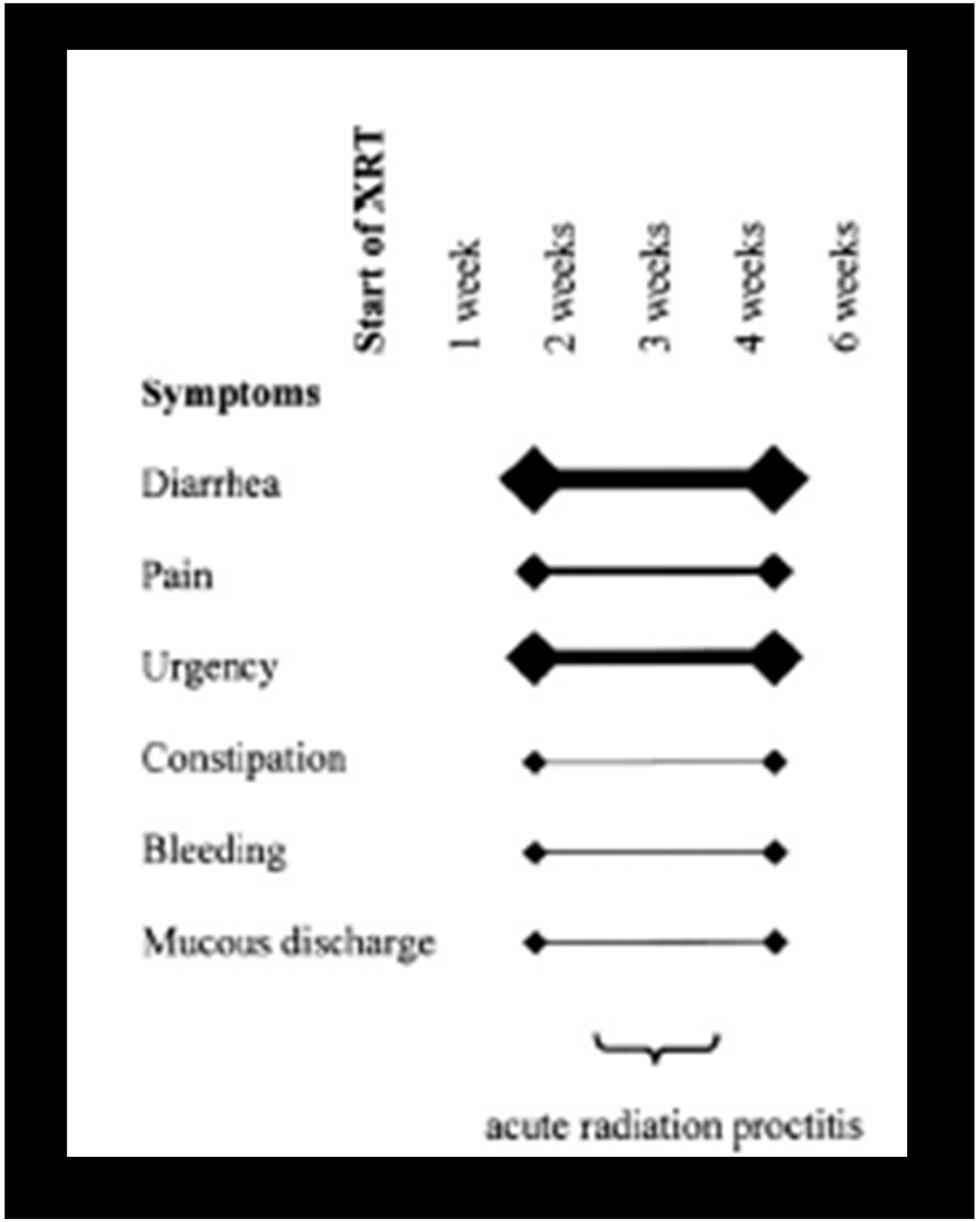
Grade IV

- Sub acute or acute obstruction / fistula / perforation
- GI bleed, needs transfusion
- Abdomen pain / Tenesmus, needs bowel diversion or tube decompression.

Acute GI effects

- Mild effects due to radiation 6 - 37.5 %
- Severe effects, 0 – 10 %, interrupts treatment
- Weekly evaluation 90 – 95 % ≤ grade II

Acute GI effects



Acute GI effects

IMRT

Grade 0	34%
Grade 1	39%
Grade 2	27%
Grade 3	-

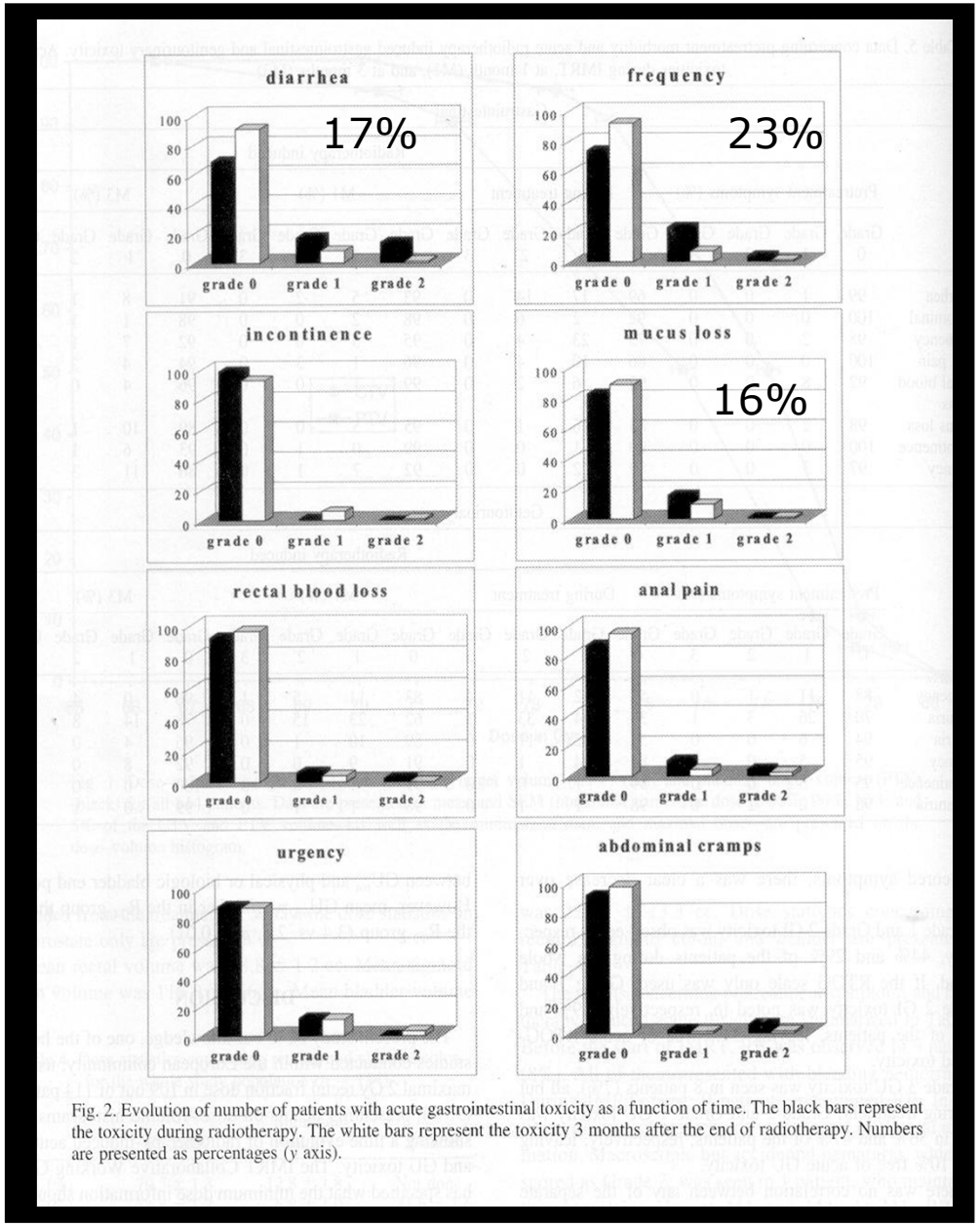


Fig. 2. Evolution of number of patients with acute gastrointestinal toxicity as a function of time. The black bars represent the toxicity during radiotherapy. The white bars represent the toxicity 3 months after the end of radiotherapy. Numbers are presented as percentages (*y* axis).

De Meerleer etal., IJROBP 2004, 60, 777

Acute GI effects

N = 306, GETUG, Multicentre, France, 3DCRT, 70 vs 80 Gy

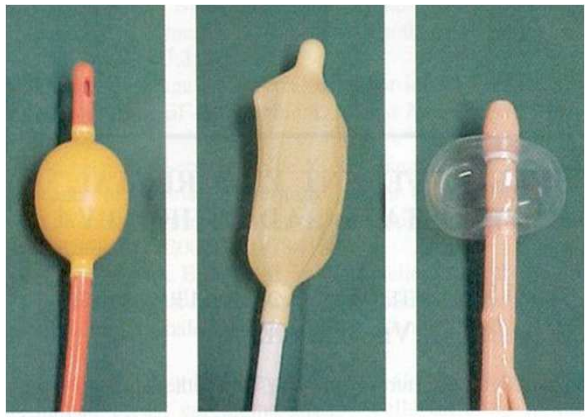
Grade	70 Gy, n=153	80 Gy, n=153
0	42	50
1	66	57
2	42	43
3	3	3

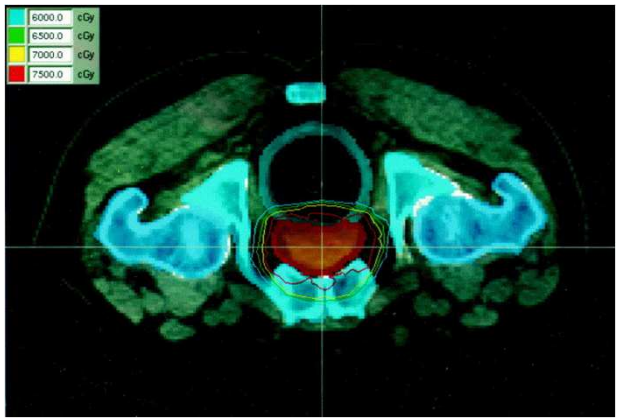
- GI acute effects 70 %
- Increases with increase in CTV
- No treatment interruption

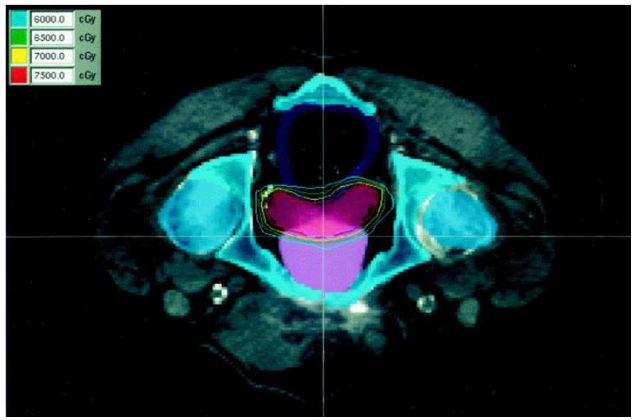
Beckendorf V et al., IJROBP, 2004, 60, 1056

Acute GI effects

Intrarectal balloon, N 100, IMRT 75.8 Gy







Grade 0	83%
Grade I	11%
Grade II	6%

Teh BS etal. IJROBP, 2001, 49, 705

Acute GI effects

3DCRT(1997 – 2002), 72 Gy/40f, n=51

P.D. Hinduja National Hospital, Mumbai

Rectal Toxicity (RTOG)	
Grade 0	4
Grade 1	31
Grade 2	16

Kannan V et al, JCRT, 2005, 1, 34

Acute GI effects, Pathophysiology

Rectal mucosa

- Edema, Hyperemia, Excess Mucus
- Acute inflammatory cells (eosinophil, mast cell) in lamina propria
- Crypt abscess

The severity of histological changes peaks at 2 weeks and improves at 6 weeks despite increase in severity of symptoms

Late GI effects

Late GI effect, RTOG grade

Grade I

- mild diarrhea/cramp
- bowel movement ≤5/day
- slight rectal discharge/bleed

Grade II

- mild diarrhea & colic
- bowel movement >5/day
- excess rectal discharge/ intermittent bleed

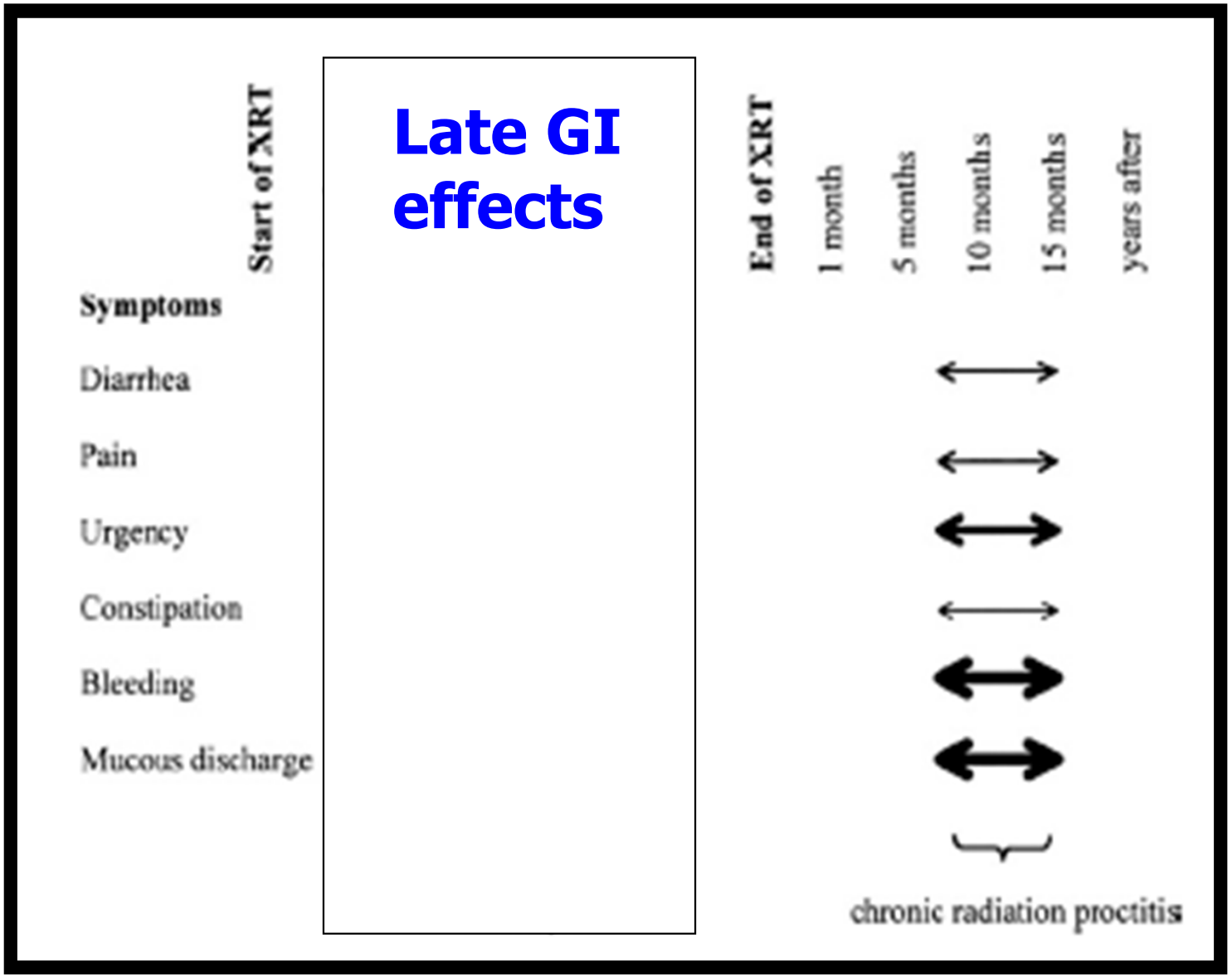
Grade III

- obstruction/bleed requiring surgery

Grade IV

- Necrosis/perforation/fistula

Late GI effects



Late GI effect, pathophysiology

- Mucosa: flattened surface epithelium
- Submucosa: myxoid change, edema, hyaline fibrosis, atypical plump fibroblasts
- Vascular changes: atypical endothelial cells, intimal fibrosis, lipid deposition, intraluminal thrombosis, adventitial fibrosis
- Telangiectasia

Late GI effect, Ano-rectal physiology

Manometric study of ano-rectal mucosa shows decreased

- sensory threshold
- maximum tolerated volume
- voluntary squeeze
- basal resting pressure

leading to fecal urgency

Epithelial, vascular, extracellular components and enteric nervous system all contribute to late injury

Late GI effect

Risk factors

1. Presence of anal symptoms prior to treatment
2. Older age
3. Diabetes
4. Acute GI effects
5. Dose/2D/3DCRT
6. Rectal dose volume
7. Anal dose volume
8. IMRT
9. Hypofraction

1. Anal symptoms

Late GI effect

Pretreatment presence of GI symptoms increases the risk of post treatment GI morbidity

Borghede G et al, RT&Oncol, 1997, 43,139
Peeters ST et al IJROBP, 2006, 64, 1151

2. Older age

Late GI effect

Older patients have higher risk of grade II rectal bleed

N=171, 3DCRT-64.8 to 81 Gy, T1-T3, MSKCC

Late rectal grade II bleeding patients were slightly older than non-bleeding patients
(69.7 vs 68.3)

Skwarchuck MW et al, et al IJROBP, 2000, 47, 103

3. Diabetes mellitus (DM)

Late GI effect

N=52, 69Gy at 3Gy/f, PTV-prostate, 4field

- Age
- T stage
- DM
- Dosimetric factors studied

Only DM was significant for late grade ≥2 toxicity

Akimoto et al, et al IJROBP,2004, 60, 1033

Late GI effect

N 1571, T1-T3, 3DCRT / IMRT, 68 – 81 Gy (MSKCC)

Acute morbidity	Late morbidity
≥ 2	42 %
< 2	9 %

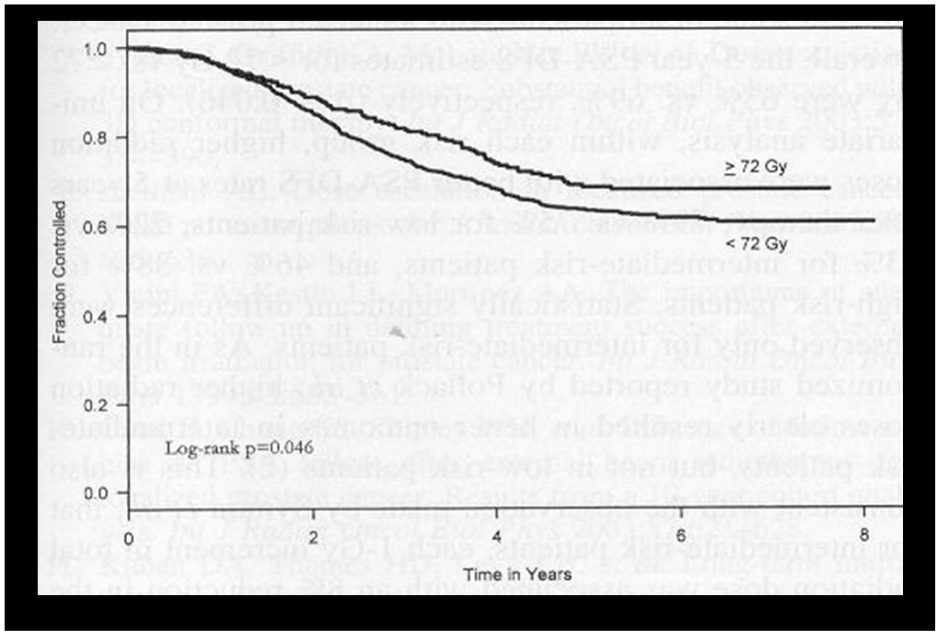
acute GI ≥ II, increased late G-II

Zelefsky MJ et al, IJROBP, 2008, 70, 1124

5.0 Dose

Late GI effect

Prostate cancer, Dose response



9 institutions data

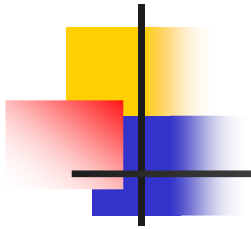
1994-1995, N=1325, T1,2
Median follow-up =5.8 years

8 year PSA DFS = 62%

Dose ≥72Gy : improves outcome

Kupelian P et al, IJROBP,2005 61, 415

Late GI effect



Severe proctitis / necrosis/ fistulae / stenosis

- $TD_{5/5}$ 60 Gy for entire rectal circumference
- $TD_{50/5}$ 80 Gy

Emami et al, 1991

Minimal late risk with 50 to 60 to posterior rectal wall

Risk of late complication increases with

1. Post. Rectal wall dose 65-70 Gy
2. Ant rectal wall dose 75 Gy

Late GI effect

Standard dose

Conformal Therapy reduces risk of grade II and III proctitis compared to conventional therapy

Nguyen LN et al, Urology, 1998, 51, 991
Sandler HM et al, IJROBP, 1995, 33, 797
Schultheiss TE et al, IJROBP, 1995, 32, 643

N 225, 2D vs 3D, 64 Gy

Remaining free of ≥ grade II proctitis, 5years

2D	3D
82 %	92 %

RMH, Dearnaley DP, Lancet, 1999, 353, 267

5.3.1 Dose, 3DCRT

Late GI effect

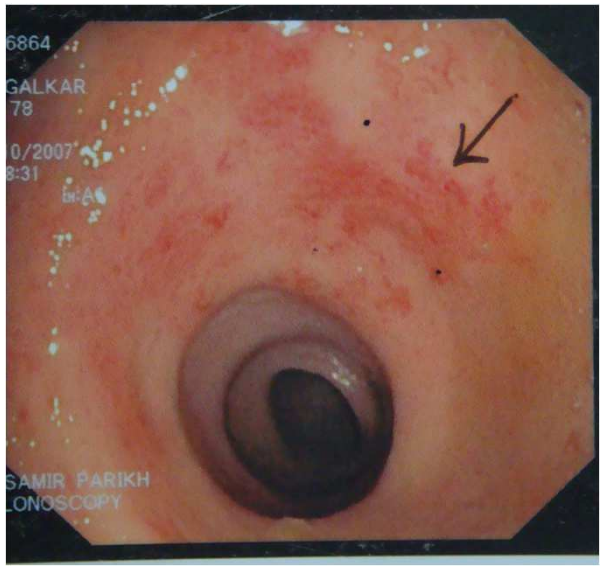
Prospective study

3DCRT(1997 – 2002), 72 Gy/40f, n=51

P.D. Hinduja National Hospital, Mumbai

Rectal Toxicity (RTOG)

Grade 0	41
Grade 1	3
Grade 2	5



Kannan V et al, JCRT, 2005, 1, 34

Late GI effect

5.3.2. Dose, 3DCRT

Prospective study

3D-CRT, RTOG 9406, 78 Gy, n=218,

Late ≥Grade 2 Rectal complication: 30 – 33%

Michalski JM et al, IJROBP, 2005, 62, 706

Late GI effect

5.3.3. Dose, 3DCRT

Prospective study

Fox Chase Cancer Center

n=230, Dose 63-79 Gy

75-76 Gy : Grade 2 - 32%

Hanks GE et al, IJROBP, 1998, 41, 501

Late GI effect

5.3.4. Dose, 3DCRT

Prospective study

N 1571, T1-T3, 3DCRT, MSKCC

Grade II - 9% at 10 years

70.2, 3D	75.6, 3D
7%	18%

Zelefsky MJ et al, IJROBP, 2008, 70, 1124

Late GI effect

5.3.5. Dose, 3DCRT

Prospective randomized study

Higher dose increases morbidity – 3DCRT

MGH Boston, Loma Linda

Zietman AL etal, JAMA, 294, 1233, 2005

70.2 GyE	79.2 GyE
8%	17%

MRC RT01, UK

Dearnaley DP etal, Lancet Oncol, 2007, 8, 475

64 Gy	74 Gy
24%	33%

MD Anderson Hospital

Kuban etal, IJROBP,2008, 70, 67

70 Gy	78 Gy
13%	26%

Late GI effect

N=124, 3DCRT, 70 Gy

Rectal volume receiving ≥ 70 Gy (V_{70})
was most predictive of grade2 morbidity

V70 < 20%	37%
V70 ≥20%	61%

van der Laan etal, IJROBP, 2008, 70, 1138

Late GI effect

	Rectal dose volume
Vargas et al, 2005	V70 >40%
Kuban et al, 2003	V70 ≥26%
Huang et al, 2002	V70 ≥26.2%
Storey et al, 2000	V70 >25%

Storey NR etal, IJROBP, 2000, 48, 65

Late GI effect

Rectal volume with doses < 60 Gy might be more strongly associated with rectal morbidity

1. At prostate dose 70.2 – 75.6 Gy when 50% isodose encompasses entire rectal volume at isocentre slice – higher grade II bleeding (1)
2. Grade II or more morbidity for V32 for rectal wall ≥ 80 % (2)

1. Skwarchuk MW et al, IJROBP, 2000, 47, 103
2. Tucker SL et al, IJROBP 2004, 60, 1589

Late GI effect

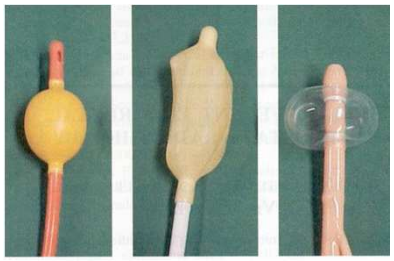
1. A new class of NTCP models called “cluster models” have been developed in which spatial distribution of dose to normal tissue (rectum) is taken explicitly into account.

2. The size of rectal wall exposed to doses between 27 and 43 Gy, with cluster model analysis, was found to be significantly associated with late GI effect

Tucker SL et al IJROBP 2006, 64, 1255

Late GI effect

Endorectal balloon (ERB)



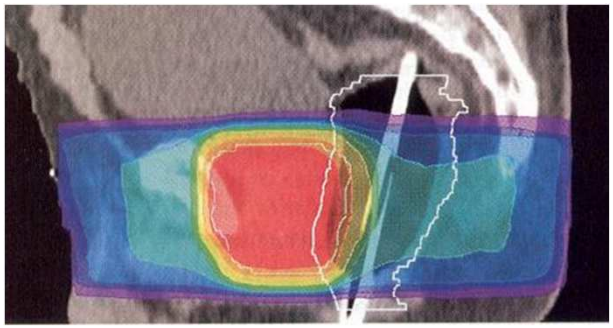
1. Reduced rectal volume exposed to >40Gy

2. Reduction in late rectal mucosal changes

3. Reduction in late rectal toxicity

6.5 rectal dose volume

- ERB pushes the lateral and posterior wall away from high dose region
- Air filled ERB may cause additional dose reduction to superficial anterior rectal mucosa because of dose build up effect without under dosing prostate gland

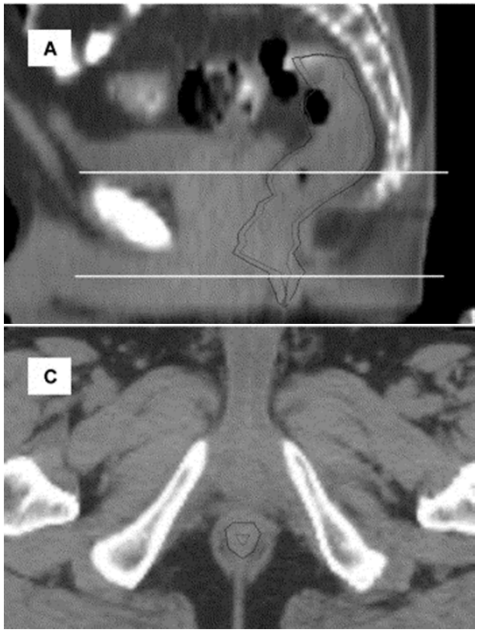


Th.van Lin ENJ et al, IJROBP, 2007, 67, 799

Late GI effect

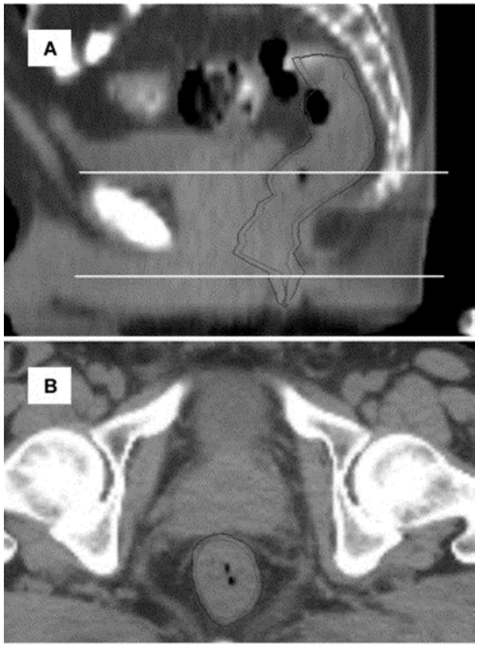
Incontinence requiring pads

- mean anal wall dose > 33 Gy
- no correlation to rectal dose



Peeters ST et al IJROBP, 2006, 64, 1151

7. Anal dose volume



Late rectal bleed - correlates with anorectal V65dosimetry (relative wall volume receiving 65 Gy)

- V65 < 30% - reduced risk of bleed
- V65 increase from 19 to 43% bleed 1 to 9%

Late GI effect

N 1571, T1-T3, 3DCRT / IMRT, 68 – 81 Gy (MSKCC)

Grade II 9% at 10 years

70.2, 3D	75.6, 3D	81, IMRT
7%	18%	**5%**

	IMRT	**3D-CRT**
Target volume coverage (81 Gy)	98%	95%
% of rectal wall – 75 Gy	**9%**	13%

IMRT reduced late g – II Rectal morbidity

Zelefsky MJ et al, IJROBP, 2008, 70, 1124

Late GI effect

Prospective IMRT studies

Author	Patient no.	Dose fraction	FU (mo)	Grade II morbidity
De Meerleer et al, 2007	133	74 – 76 Gy	36	17 %
Vora et al, 2007	145	75.6 Gy	48	23 %

Cahlon O et al Semin Radiate Oncol 2008, 18, 48

Late GI effect

Prospective hypofractionation studies

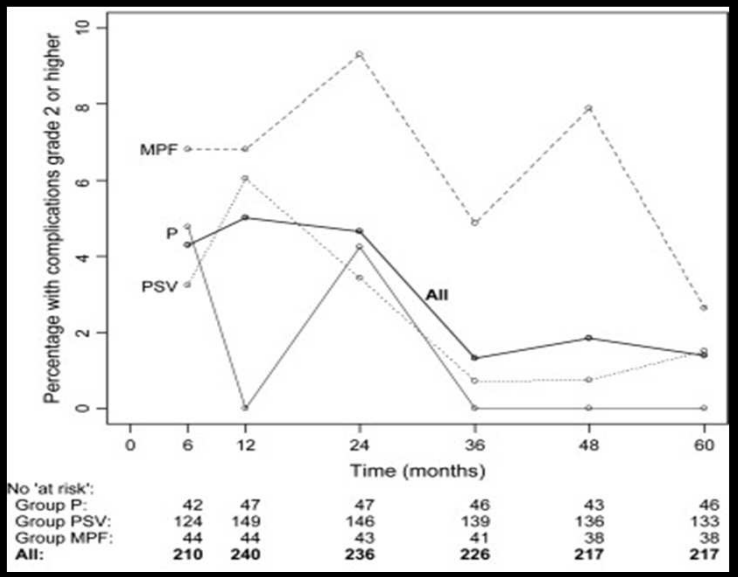
Author	Patient no.	Dose fraction	NTD_{2Gy} ($\alpha/\beta - 1.5$)	Grade II morbidity
Kupelian, 2007	770	70 Gy / 2.5 Gy	80 Gy	**4.5** %
Tsuji, 2005 *	201	66 GyE / 3.3 GyE	90.5 Gy	**1** %
Martin, 2006	92	60 Gy / 3 Gy	77 Gy	**2** %
Madsen, 2007	40	33.5 Gy / 6.7 Gy	78.5 Gy	**7.5** %

*** C ion, 4f / week, daily CT imaging, daily bladder filling and rectal enema – no ≥ grade III toxicity**

Miles EF et al Semin Radiate Oncol 2008, 18, 41

Late GI effect

Late GI morbidity fades with time



Karlsdottir H et al, IJROBP, 2008, 70, 1478

RT + hormones:
RTOG 8531, 8610, 9202
N=2922, follow up 10.3 years

Short course hormone, neoadjuvant + concurrent shows lesser grade III morbidity

Lawton CA et al, IJROBP, 2008, 70, 437

Treatment of radiation proctitis: acute

Amifostine, s.c & intrarectal, was found to reduce acute rectal morbidity

SynodinouMenegaki M et al, IJROBP, 2002, 64, s268
Singh AK et al IJROBP, 2006, 65, 1018 & 2008,70, 90

Treatment of radiation proctitis: late

1. **Sucralfate / steroid** enema,
2. **Sulfasalazine** oral
3. **Pentosan-polysulfate**, (fibrinolytic anti-inflammatory mucoprotective)
4. **Formalin** application to the rectal mucosa
5. **Laser** therapy (**Argon**, Nd:YAG) Risk: transmural necrosis
6. **Butyric acid** (short chain fatty acid) enema

Surgical fecal diversion

Treatment of radiation proctitis: late

Animal studies

1. Late radiation intestinal morbidity – stromal accumulation of fibrogenic mediator connective tissue growth factor (CTGF). It acts through Rho/Rho cell signaling pathway
   Pravastatin (a statin) inhibits Rho isoprenylation and CTGF. (1)

2. RT -> endothelial injury through loss of thrombomodulin (TM)
   Simvastatin upregulates TM, with protection of endothelium & reduction of late effects. (2)

1. Haydont V et al, IJROBP, 2007, 68, 1471
2. Wang J et al, IJROBP, 2007, 68, 1483

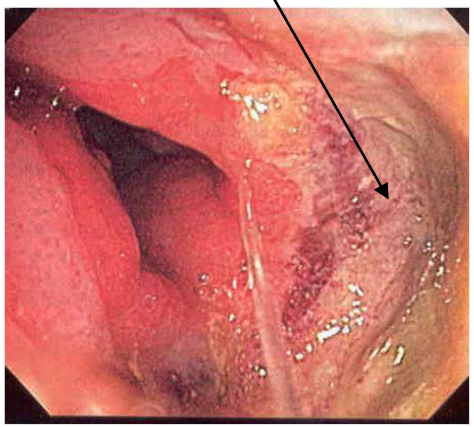
Treatment of radiation proctitis: late

Hyperbaric oxygen

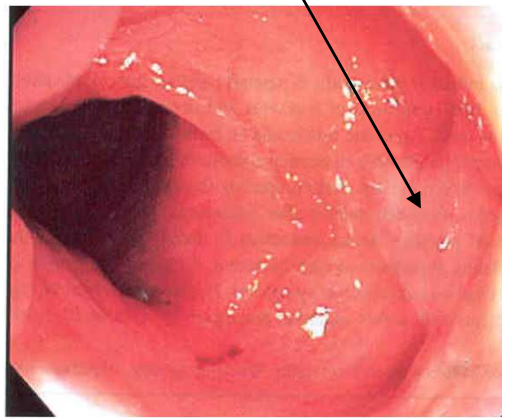
- Improvements observed for incontinence, diarrhoea, bleeding and pain
- Incontinence and mild bleeding resolve the most

Woo TCS et al, IJROBP, 1997, 39, 690

Rectal ulcer, post RT



After HbO treatment



Nakabayashi M et al, Urol Oncol Semin, 2006, 24, 503

Acute GU effects

Acute GU effects - RTOG grade

Grade I

- Frequency/nocturia twice pre RT
- dysuria

- No drugs required

Grade II

- Frequency/nocturia less frequent than hrly
- Dysuria, spasms

- Needs drugs , occasional narcotis

Grade III

- Frequency/nocturia hourly or more
- Dysuria, pain, spasms - frequent narcotis
- Gross hematuria, needs transfusion
- Catheter for urinary obstruction/clots

Grade IV

- Gross hematuria, needs > 1 transfusion
- Hospitalization for sepsis due to obstruction, ulcer, necrosis of bladder

Acute GU effects

- Acute GU symptoms – appears in 3rd week of RT (frequency, nocturia, urgency, dysuria)
- 60 % require medication

Dose (Gy)	Acute GU morbidity	
	Grade III	Grade IV
70	3%	1%
78	4%	1%

Acute morbidity correlates with percentage of bladder treated to ≥ 70 Gy

Storey MR et al et al, IJROBP, 2000, 48,635

Acute GU effects

N 114, IMRT, 74 – 78 Gy, Belgium

G 0	10 %
G I	47 %
G II	36 %
G III	7 %

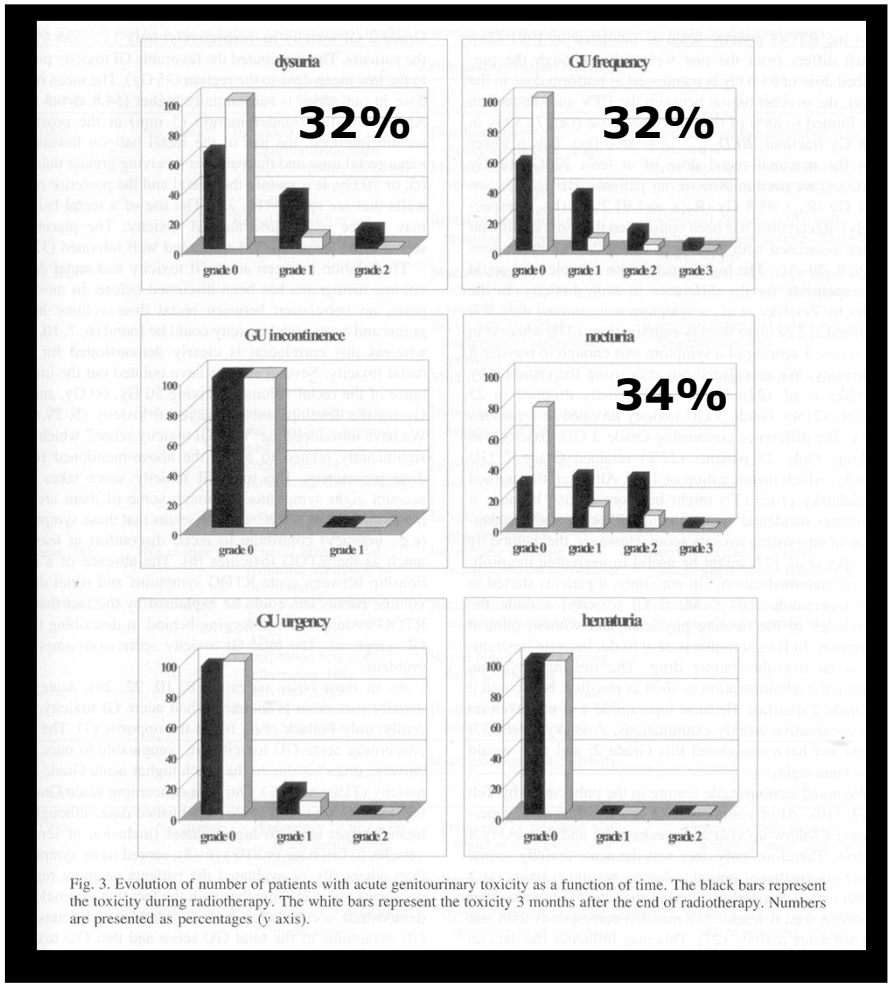


Fig. 3. Evolution of number of patients with acute genitourinary toxicity as a function of time. The black bars represent the toxicity during radiotherapy. The white bars represent the toxicity 3 months after the end of radiotherapy. Numbers are presented as percentages (*y* axis).

1. More pronounced than GI morbidity
2. Higher with increasing dose
3. Cause- urethral/bladder neck inflammation

De Meerleer G et al, IJROBP, 2004, 60, 777

Acute GU effects

3DOG / RTOG 9406, 68.4 / 73.8 Gy

Acute GU effect increases with neo adjuvant + concurrent hormone therapy

Michalski JM etal, IJROBP, 2000, 46, 391

De Meerleer etal., IJROBP, 60, 777-87,2004, Belgium

Late GU effects

Late GU effects - RTOG grade

Grade I

- Slight epithelial atrophy
- Minor telangiectasia
- Microscopic hematuria

Grade II

- Moderate frequency
- Generalized telangiectasia
- Intermittent microscopic hematuria

Grade III

- Severe frequency & dysuria
- Generalized telangiectasia (petechiae)
- Frequent hematuria
- Reduction in bladder capacity (<150cc)

Grade IV

- Necrosis
- Bladder capacity <100cc
- Severe hemorrhagic cystitis

Late GU effects

RTOG 7506 , 7706, N= 1020 patients,
hospitalization due to chronic urinary sequelae (cystitis, hematuria, urethral stricture, bladder contracture) occurred in 7.3% patients.

Surgical intervention due to urinary toxicity - in 0.5%.

The commonest late urinary complication was urethral stricture occurring mostly in patients with previous TURP

Late GU effects

Prospective studies

Bladder, urethral morbidities $\geq$ grade 2 do not show any consistent increase in incidence at escalated dose compared to standard dose

Late GU effects

Prospective randomized studies

Higher dose no increase in morbidity – 3DCRT

MGH Boston, Loma Linda

Zietman AL etal, JAMA, 294, 1233, 2005

70.2 GyE	79.2 GyE
18%	20%

MRC RT01, UK

Dearnaley DP etal, Lancet Oncol, 2007, 8, 475

64 Gy	74 Gy
6%	8%

Dutch multicentre

Peeters et al JCO, 2006, 24, 1990

68 Gy	78 Gy
41%	39%

Late GU effects

N 1571, T1-T3, 3DCRT / IMRT, 68 – 81 Gy (MSKCC)

At 10 years ≥grade II – 15%

81 Gy - 20%

< 81 Gy - 12 %

Occurrence of acute GU morbidity ≥2 significantly increased late GU toxicity

Zelefsky MJ et al, IJROBP, 2008, 70, 1124

Late GU effects

N= 331, 3DCRT - 75.6Gy (Michigan)

<u>Strong predictors for chronic GU toxicity</u>

1.Acute urinary toxicity

2.Bladder dose-volume

Harsolia et al, et al, IJROBP, 2007, 69,1100

Erectile tissue dysfunction (ED)

Erectile tissue dysfunction

There is a fall in potency after curative RT

N=743, post RT likelihood of potency loss 60%

Zelefsky MJ et al, Cancer, 1999, 85, 2460

N=268, 3DCRT, 68 to 78 Gy
3 years post RT only 38 % had potency

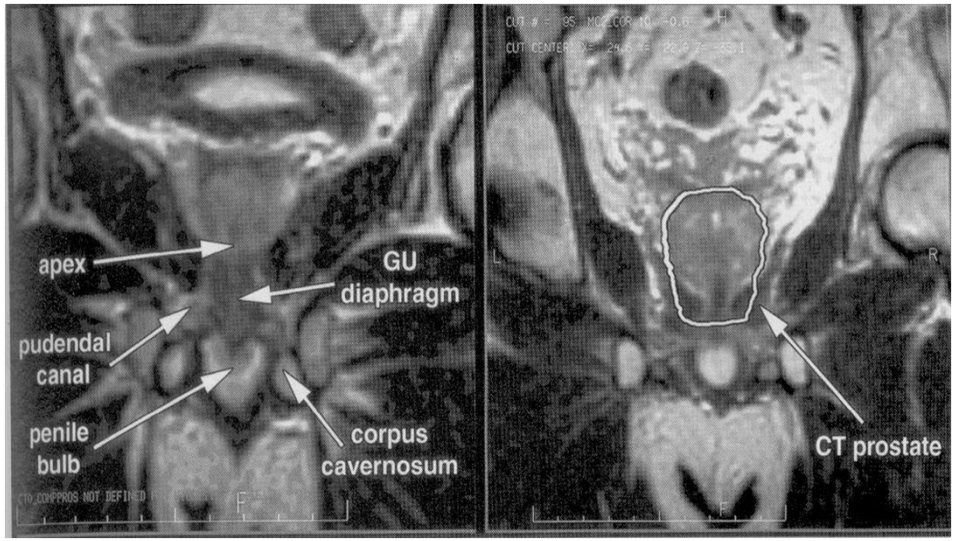
Van der Wielen GJ et al, et al, IJROBP, 2007, 68, 479

Erectile tissue dysfunction

Cause of ED : RT to penile bulb & vascular tissue (CC)

MRC RT01: Penile Bulb - D50 $\geq$ 60 Gy,
significant risk of Erectile dysfunction

Stephen M etal., IJROBP, 2005 ,63, S126,

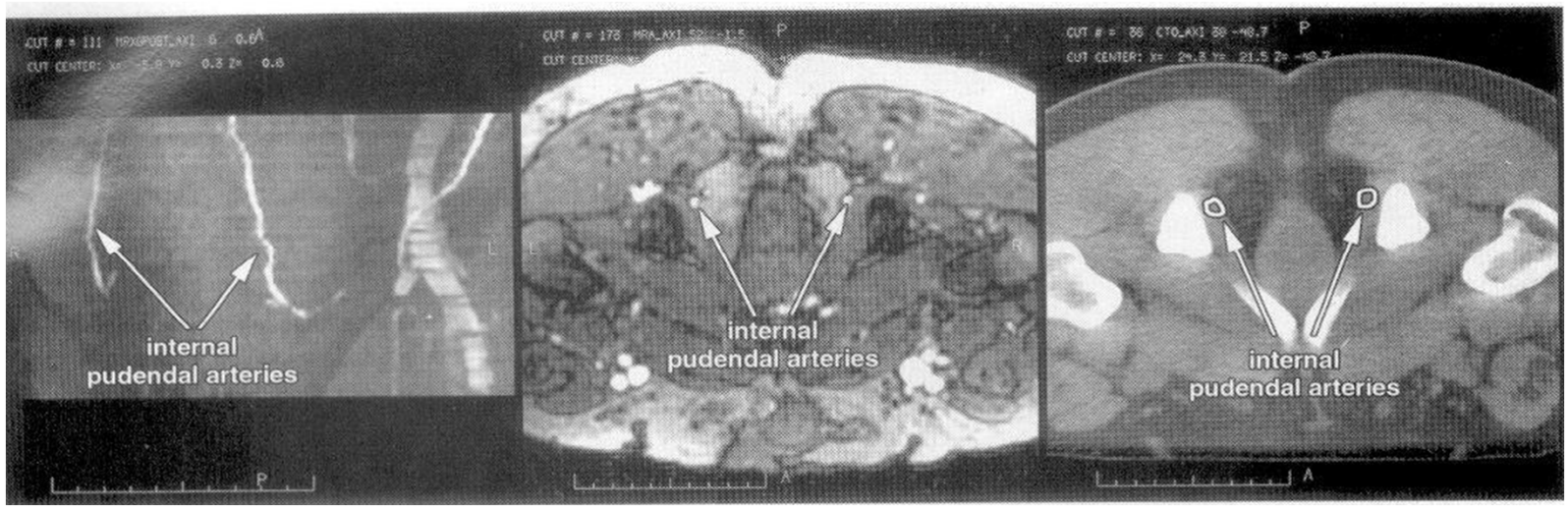


McLaughlin PW etal., IJROBP, 2005, 61, 20-31, Michigan

Erectile tissue dysfunction

N-10, IMRT 80 Gy, Vessel sparing protocol, MRI & CT

Time-of-flight MRI angio to define Int.pud.artery(IPA)



- D_{50} for IPA 35 Gy
- 70% of PB 9.7 Gy

McLaughlin PW etal., IJROBP, 61, 20-31, 2005, Michigan

Thank You